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Safety of a topically applied spot-on formulation of metaflumizone plus amitraz for flea and tick control in dogs

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Abstract

Four laboratory studies were conducted in Beagle dogs to evaluate the safety of a novel ectoparasiticide combination of metaflumizone plus amitraz (ProMeris®/ProMeris Duo® for Dogs, Fort Dodge Animal Health, Overland Park, KS) when applied according to the recommended dosage of ≥20 mg metaflumizone kg^{-1} plus ≥20 mg amitraz kg^{-1}, at exaggerated and repeated dosages, and if accidentally orally ingested. Parameters evaluated included body weight, food consumption, clinical, physical and neurological examinations, clinical pathology and gross and microscopic pathology. Exaggerated and repeated topical treatment with metaflumizone plus amitraz administered at 1×, 3× and 5× the recommended dose had no effect on clinical findings, heart rates, body weight, food consumption, physical/neurological examinations, macroscopic and microscopic pathology. Very slight, transient, clinically insignificant increases in serum urea nitrogen were noted in some dogs treated at all dose rates tested. This effect was not persistent, was not dose-responsive, nor aggravated by repeated applications and was not associated with a corresponding increase in creatinine or renal pathology. Therefore, these increases in urea nitrogen were suspected to be of non-renal origin and were not considered toxicologically significant. Exaggerated doses (3× and 5×) caused very mild, transient hyperglycemia, most notably in some adult females. Transient and inconsistently noted mild increases in leukocytes, neutrophils and monocytes were observed in some 3× and 5× treated dogs at some intervals. None of the effects noted were aggravated by repeated administration. When 10% of the recommended topical dose was orally administered to mimic exposure due to licking the application, avoidance behaviors including spitting, head shaking, and salivation were noted immediately in all animals. Consequently, voluntary oral ingestion is considered unlikely. Transient decreased activity, slightly reduced body temperature and pale oral mucous membranes were noted in some animals beginning 1–2 h posttreatment. Ataxia, resolving within 4 h posttreatment, was noted in one female. Oral administration had no effect on clinical pathology. Results from these four studies indicate repeated use of metaflumizone plus amitraz causes no adverse health effects when used as recommended in dogs as young as 8 weeks of age.

Keywords: ProMeris®; ProMeris Duo®; Metaflumizone; Amitraz; Dog; Safety; Semicarbazone

1. Introduction

ProMeris®/ProMeris Duo® for Dogs (15% (w/v) metaflumizone plus 15% (w/v) amitraz, Fort Dodge Animal Health, Overland Park, KS) is an ectoparasiticide combination in a topical spot-on formulation intended for flea and tick control on puppies and dogs. Metaflumizone is a novel insecticide in the semicarbazone class of chemistry that acts as a sodium channel antagonist and disrupts nerve function resulting in paralysis and death of insects (Salgado and Hayashi, 2007). It has no known cross-tolerance in insecticide resistant strains (Klein and

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Oloumi, 2005) and has demonstrated excellent efficacy against fleas (Holzmer et al., 2007). In the formulation, metaflumizone is combined with amitraz, an acaracide, to provide activity against both fleas and ticks (Rugg and Hair, 2007). Dogs are treated according to weight bands designed to provide a minimum dose rate of 20 mg metaflumizone kg^{-1} plus 20 mg amitraz kg^{-1}.

Metaflumizone has not previously been used in veterinary medicine. In studies of mammalian toxicity, metaflumizone was characterized as having very low acute toxicity (rat oral and dermal acute LD_{50}s are >5000 mg kg^{-1}) and relatively low toxicological potential following subchronic oral exposure in rats, mice and dogs (Hempel et al., 2007). Reduced weight gain and decreased food consumption were the primary observable adverse effects in dogs treated orally for 12 months at 30 mg kg^{-1} day^{-1} (EPA, 2006). Amitraz is currently approved for use in topical applications for both food producing and companion animals. Amitraz is generally classified as an inhibitor of the enzyme monoamine oxidase, which is responsible for degrading the neurotransmitters norepinephrine and serotonin. In mammals, reported clinical effects are due primarily to its α-2-adrenoceptor agonist activity (EMEA, 1996). In dogs, signs of toxicosis include lethargy, hyperexcitability, vomiting, CNS depression, ataxia, hypothermia, transient bradycardia, hypotension or hypertension and hyperglycemia (EPA, 1975; EMEA, 1996; Hugnet et al., 1996; Plumlee, 2004). These effects generally resolve without intervention, are rarely fatal and can be reversed with α-2-adrenoceptor antagonists such as atipamezole (Hugnet et al., 1996).

Four studies were conducted to evaluate the safety of metaflumizone plus amitraz in dogs 8 weeks of age and older. Two studies (Studies 1 and 2) of similar design, one in adult dogs and one in 8-week-old puppies, were conducted to evaluate the safety of a single topical application of 1×, 3×, or 5× the proposed commercial dose ($\geq$20 mg metaflumizone kg^{-1} plus $\geq$20 mg amitraz kg^{-1}) compared to placebo-treated animals. Study 3 evaluated the effect of metaflumizone plus amitraz in 10-week-old puppies administered seven topical applications of 1×, 3×, or 5× the proposed commercial dose at 2-week intervals. Study 4 was conducted to evaluate the safety and behavioral responses following inadvertent oral exposure. In this study, dogs were evaluated after oral administration of 10% the recommended dose, the amount that estimates potential oral exposure due to licking after topical application.

2. Materials and methods

Each study was conducted in accordance with the Organization for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice (GLP) (OECD, 1998) ENV/MC/CHEM(98)17 and/or in accordance with GLP Standards as set forth by EPA in 40 Code of Federal Regulations (CFR) Part 160 (FIFRA).

2.1. Animals

All studies were performed with purpose-bred Beagles. Mature dogs (Studies 1 and 4) were at least 6 months of age and weighed from 5.16 to 12.02 kg at study initiation. Puppies used in the single dose study (Study 2) were 8 weeks of age and weighed 1.64–2.81 kg at the time of treatment. Puppies used in the repeated treatment study (Study 3) were 10 weeks of age and weighed 2.00–4.36 kg at the time of first treatment. In Studies 1 and 2, 24 male and 24 female animals were ranked by weight within gender, blocked into groups of four and randomly assigned to four treatment groups of 12 animals in each study. In the repeated treatment study (Study 3), 16 males and 16 females were ranked by weight within gender, blocked into groups of 4 and randomly assigned to 4 treatment groups of 8 animals. In the oral exposure study (Study 4), eight male and eight female young, purpose-bred adult Beagle dogs were ranked by weight within gender, blocked into groups of two and randomly assigned to two treatment groups of eight animals.

2.2. Housing and care

Adult dogs were individually housed in cages and puppies individually housed in runs according to animal welfare regulations (Guide for the Care and Use of Laboratory Animals, rev. 1985, National Institutes of Health; Animal Welfare Act, USDA/APHIS). Solid cage walls and partitions prevented contact between animals. Dogs and puppies were fed an age appropriate maintenance ration of a commercial dry canine feed with water available *ad libitum*. All animals were observed at least twice a day for morbidity, mortality, injury, and the availability of food and water.

2.3. Formulation and dosage

For all studies the commercial formulation containing 15% (w/v) metaflumizone plus 15% (w/v) amitraz was used. Dogs were treated at multiples of the